REMARKS

Claim 1 has been amended. Claims 1-15, 17, 29-31, and 36-48 are now pending. Reconsideration is respectfully requested in view of the following remarks.

I. Claim Rejections Under 35 U.S.C. 112, First Paragraph

The Examiner rejected claims 1-15, 17, 29-31, and 36-48 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner asserted that the specification does not provide support for the term "liquid particles." In the interest of expediting prosecution of the application, Applicant has deleted this term. Applicant believes that this rejection is now moot and respectfully requests its withdrawal.

II. Claim Rejections Under 35 U.S.C. 103(a):

The Examiner rejected claims 1-15, 17, 29-31, and 36-48 under 35 U.S.C. 103(a) as being unpatentable over Nyce (5,527,789) in view of Ansel et al. (Pharmaceutical Dosage Forms and Drug Delivery System, page 454-455).

Applicant respectfully asserts that the Examiner has not demonstrated that claims 1-15, 17, 29-31, and 36-48 are *prima facie* obvious. To establish a *prima facie* case of obviousness, "... there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or combine reference teachings." See MPEP 2143. In this case, there is no "suggestion or motivation" in Nyce (5,527,789) or Ansel to combine these references. Particularly, these references do not teach the small particle size compositions of dehydroepiandrosterones or pharmaceutically or veterinarily acceptable salts thereof and ubiquinone.

The presently claimed invention pertains to the dehydroepiandrosterone type agent and ubiquinone in a composition having a defined particle size range. The claimed composition will provide localized treatment in a high, non-systemic manner that is not taught or suggested by Nyce (5,527,789) or Ansel.

Also, there is no "knowledge generally available to one of ordinary skill in the art" to combine or modify the cited references. As the attached copy of the declaration from Dr. Cynthia B. Robinson, filed in copending application Serial No. 10/072,010, demonstrates, a person of skill in the art would have believed that local administration of a dehydroepiandrosterone type compound in small particle size to asthma patients would have unacceptable side-effects due to systemic absorption of the drug. Contrary to these beliefs, as Dr. Robinson's declaration demonstrates, a sample dehydroepiandrosterone compound, DHEA-S, in small particles produces high local concentrations and without producing high systemic levels. Thus, due to a lack of suggestion in the references or in the art to combine or modify the references, Applicant respectfully asserts that Examiner has not made a *prima facie* case of obviousness.

Further, references can be combined or modified to make a prima facie case of obviousness as long as there is "a reasonable expectation of success." See MPEP 2143.02. In this case, Applicant respectfully asserts that there is no "reasonable expectation of success" to combine or modify Nyce (5,527,789) or Ansel. This is because one skilled in the art would expect that small particles of the active agent would not be suitable for treatment as these particles would be expected to be absorbed systemically and thus produce unacceptable side-effects to the patients being treated. However, the contrary was observed, as evidenced by Dr. Robinson's declaration, that is the small DHEA-S particles were essentially not absorbed systemically.

Although it is known in the art that a drug could possibly be administered to the respiratory system by reducing its particle size, what is unexpected herein is that dehydroepiandrosterones, such as DHEA-S, and ubiquinone as a respiratory agents will produce high local concentrations of the agents in the lung and bronchial areas with low systemic levels, thus, allowing for a desired therapeutic effect in the lung and bronchial areas with minimal systemic side effects. For example, it would be expected that respirable particles would enhance systemic uptake of a drug by taking advantage of the very large surface area of the lung and very thin barrier to drug diffusion. Due to this systemic absorption from the lung, it would be expected that during the development of DHEA-S as a respiratory drug significant metabolism to DHEA would be observed along with secondary effects on sex organs, hematocrit and muscle mass. In Dr. Robinson's toxicology studies in dogs, up to 3.54 mg/kg/day of drug blend was administered as a dry powder to the respiratory tract for 3 months. The data show that there was approximately a 3,000-fold increase in the lung over

endogenous circulating levels of DHEA-S but no measurable increase in DHEA over endogenous levels in dogs. There was no change in sex organ weights nor increases in muscle mass or hematocrit, demonstrating low systemic effects of the drug. In clinical studies, up to 17 mg/day of DHEA-S was administered for 13 days to the respiratory tract. A modest, but clinically insignificant, increase in circulating levels of DHEA-S was observed but no increase in DHEA, sex hormone binding globulin or testosterone. Thus, contrary to expectations, the respirable particle size of DHEA-S did not enhance the systemic uptake of the drug nor were systemic effects noted in toxicology studies or clinical studies. Thus, although it is known that particle size is important to respiratory tract delivery, it would not be anticipated or expected that DHEA-S (and by extension) DHEA and ubiquinone would exert only a local effect and not a systemic effect. Due to these unexpected effects, Applicant asserts that Nyce (5,527,789) and Ansel are not properly combined or modified to make a *prima facie* case of obviousness of the instantly claimed invention as there was no "reasonable expectation of success." Hence, Applicants respectfully request the withdrawal of the obviousness rejection under 35 U.S.C. 103(a).

III. Double Patenting:

The Examiner has rejected claims 1-15, 17, 29-31, and 36-48 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-19 of U.S. Patent No. 5,527,789. In the interest of expediting the prosecution of the application, terminal disclaimer is being filed.

CONCLUSION

In light of the remarks set forth above, Applicants believe that they are entitled to a letters patent. Applicants respectfully solicit the Examiner to expedite the prosecution of this patent application to issuance. Should the Examiner have any question, the Examiner is encouraged to telephone the undersigned.

Respectfully submitted,

Date: April 7, 2004

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